

**AMENDMENTS TO THE DRAWINGS**

The Applicant has enclosed herewith replacement drawing for Figure 5. Specifically, the Applicant has corrected the typographical error as noted by the Examiner in the legend. As such, the Applicant submits that no new matter has been added.

## **REMARKS**

Applicant expresses appreciation to the Examiner for consideration of the subject patent application. Claims 1-79 are pending. Claims 45-79 have been withdrawn. Claims 1 and 21-25 have been amended.

Reconsideration of the application is respectfully requested in view of the following responsive remarks. For the Examiner's convenience and reference, Applicant's remarks are presented in the order in which the corresponding issues were raised in the Office Action.

In the Office Action of January 20, 2011, the following actions were taken:

- (1) The election of Group I and species (A), (B), (C,D), (E), and (G) was acknowledged;
- (2) Figure 5 was object to for having a typographical error;
- (3) Claims 1-29 and 31-44 were rejected under 35 U.S.C. 112, second paragraph as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which the applicant regards as the invention;
- (4) Claims 1-7, 12-18, 21-23, 25-27, 29, 31, 37-38, and 43-44 were rejected under 35 U.S.C. 102(b) as allegedly being anticipated by, or in the alternative under 35 U.S.C. 103(a) as allegedly obvious over, "A Metal-Chelating Pluronic for Immobilization of Histidine-Tagged Proteins at Interfaces: Immobilization of Firefly Luciferase on Polystyrene Beads" by Ho et al., *Langmuir*, 14(14), 3889-3894 (1998) (hereinafter "Ho");
- (5) Claims 1-24, 26-27, and 31-44 were rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over "Nickel-Dependent Oxidative Cross-Linking of a Protein" by Gill et al., *Chem. Res. Toxicol.*, 10(3), 302-309 (1997) (hereinafter "Gill"); and
- (6) Claim 1-24, 26-29, and 31-44 were rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over U.S. Patent No. 6,087,452 (hereinafter "Stewart") in view of "A Critical Role for Tyrosine Residues in His6Ni-Mediated Protein Cross-Linking" by Fancy et al., *Biochem. Biophys. Res. Comm.*, 247, 420-426 (1998) (hereinafter "Fancy").

It is respectfully submitted that the presently pending claims be allowed based on the remarks below.

### **Restriction/Election**

The Applicant wishes to correct an error regarding the current claims under prosecution. As noted by the Examiner, the Applicant has elected Group I (claims 1-44) and species (A), (B), (C,D), (E), and (G). The Applicant notes that claim 30 was identified by the Examiner as pertaining to Group I and specifically to species (E). Office Action dated 8/31/10, page 2 and 3. As such, the Applicant submits that claim 30 has been elected for prosecution in accordance with Applicant's election. The Applicant submits that any prior omission of claim 30 on Applicant's part was inadvertent and requests consideration of claim 30 in the current prosecution.

### **Claim Amendments**

The Applicant has amended claim 1 to remove any alleged ambiguity as suggested by the Examiner and in accordance with the specification; e.g., claim 45 and FIG 1. Claim 21 has been amended to remove the general reference to "small molecule." As such, claims 22-25 have been amended to correct antecedent basis issues caused by the removal of "small molecule" from claim 21. Additionally, claim 25 was amended to remove "derivative" and to add "fluorescent label" to CY-3 and CY-5 as suggested by the Examiner. As such, the Applicant submits that no new matter has been added.

### **Claim Rejections - 35 U.S.C. § 112, second paragraph**

The Examiner has rejected the claims as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which the applicant regards as the invention. Specifically, the Examiner alleges that claim 1 is indefinite because it is unclear as to whether the metal ligands are the same or different. Additionally, the Examiner has questioned the structure between the moieties, the phenolic groups or phenolic derivatives, and the metal ligand. Further, the Examiner questioned whether the cross-linked product is required or merely exemplary.

The Applicant has amended claim 1 to clarify the issues presented by the Examiner. Specifically, claim 1 now recites a first and second ligand as well as define the structure of the moiety, phenolic group or phenolic derivative, and the metal ligand. Additionally, claim 1 now positively recites a cross-linking step. As such, the Applicant submits that the Examiner

concerns have been addressed by the current claim amendments and respectfully requests that the Examiner withdraw the present rejection to claim 1.

Regarding claim 21, the Examiner has requested clarification regarding the term “small molecule.” The Applicant has removed the term “small molecule” from claim 21. As such, the term “small molecule” only appears in claims 22-25 where the term is subsequently defined. As such, the Applicant submits that the rejection to claim 21 is moot and that claims 22-25 properly define the term. Therefore, the Applicant respectfully requests that the Examiner withdraw the rejection to claim 21.

Regarding claim 25, the Examiner has alleged that the term “derivatives” improperly expands the scope of the Markush group. Without conceding the correctness of the Examiner’s assertion and solely to advance prosecution, the Applicant has removed the term “derivatives” from claim 25. As such, the Applicant respectfully requests that the Examiner withdraw the rejection to claim 25.

Regarding claims 40-42, the Examiner has alleged that the terms “HY-tag,” “CY-3,” and “CY-5” are unclear. Regarding “HY-tag,” the Applicant respectfully disagrees and notes that the term is defined in the current specification. Specifically, the Applicant notes that WO2005/019421, page 6, line 22 states “HY-tags refer to HIS-tags that include tyrosines therein.” Regarding “CY-3” and “CY-5,” the Applicant notes that claims 40-42 do not recite these terms. However, after review, the Applicant acknowledges that these terms are used in claim 25. As such, the Applicant has amended claim 25 to include “fluorescent label” in connection with these terms as suggest by the Examiner. In light of the above, the Applicant respectfully requests that the Examiner withdraw the rejection to claims 40-42.

### **Claim Rejections - 35 U.S.C. § 102**

The Examiner has rejected claims 1-7, 12-18, 21-23, 25-27, 29, 31, 37-38, and 43-44 as being anticipated by Ho. Before discussing the rejection, it is thought proper to briefly state what is required to sustain such a rejection. It is well settled that “[a] claim is anticipated only if each and every element as set forth in the claims is found, either expressly or inherently described, in a single prior art reference.” *Verdegaal Bros. v. Union Oil of California*, 814 F.2d 628, 2 U.S.P.Q. 2d 1051, 1053 (Fed. Cir. 1987). In order to establish anticipation under 35 U.S.C. 102, all elements of the claim must be found in a single reference. *Hybritech, Inc. v.*

*Monoclonal Antibodies, Inc.*, 231 U.S.P.Q. 81, 90 (Fed. Cir. 1986), *cert. denied* 107 S.Ct. 1606 (1987). In particular, as pointed out by the court in *W.L. Gore & Assoc., Inc. v. Garlock, Inc.*, 220 U.S.P.Q. 303, 313 (Fed. Cir. 1981), *cert denied*, 469 U.S. 851 (1984), "anticipation requires that each and every element of the claimed invention be disclosed in a prior art reference." "The identical invention must be shown in as complete detail as is contained in the...claim." *Richardson v. Suzuki Motor Co.* 9 U.S.P.Q. 2d 1913, 1920 (Fed. Cir. 1989).

Ho

Ho discloses immobilization scheme for histidine-tagged proteins using nitrilotriacetic acid (NTA)-derivatized Pluronic F108 triblock copolymers. Page 3890, 1<sup>st</sup> column, Figure 1 description. The hydrophilic NTA-modified PEO blocks extend in solution, creating an activity-preserving interface to which histidine-tagged proteins bind through chelated metal ions. *Id.* and Figure 1.

The Examiner has alleged that Ho teaches each and every element of the above referenced claims, including independent claim 1. However, the Applicant respectfully disagrees and traverses the present rejection. The Applicant notes that the present claims provide, *inter alia*, "crosslinking the first and second moieties by exposing the coordination complex to an oxidizing agent to form a covalent crosslink between the phenolic groups or the phenolic derivatives attached to each of the first and second moieties."

As such, the Applicant notes that, in addition to the formation of a coordination complex, the present method claims require a cross-linking between the phenolic groups or phenolic derivatives between the first and second moieties. Contrary to the present method, Ho does not crosslink but forms a coordination complex between the histidine tag, a metal ion, and a derivatized triblock copolymer (Pluronic F108). To be clear, Ho does not teach or disclose a phenolic group or phenolic derivative of a first moiety that is cross-linked with a phenolic group or phenolic derivative of a second moiety.

In light of the above, the Applicant submits that Ho does not teach each and every element of the present claims. As such, the Applicant respectfully requests that the Examiner withdraw the present rejection.

**Claim Rejections - 35 U.S.C. § 103**

Before discussing the obviousness rejections herein, it is thought proper to briefly state what is required to sustain such a rejection. The issue under § 103 is whether the PTO has stated a case of *prima facie* obviousness. The Applicant does not deem it necessary to recite the entire case law standard required in order to establish a *prima facie* case of obviousness. However, the Applicant would like to briefly remind the Examiner that a *prima facie* case of obviousness generally includes establishing 1) that the asserted references as modified or combined teach or suggest each and every element of the claimed invention, 2) that the asserted references as modified or combined provide a sufficient likelihood of successfully making the modification or combination, and 3) a reason for the modification or combination asserted.

Additionally, under *KSR*, and as outlined under the MPEP § 2143, additional rationales include (a) combining prior art elements according to known methods to yield predictable results; (b) simple substitution of one known element for another to obtain predictable results; (c) use of known technique to improve similar devices (methods, or products) in the same way; (d) applying a known technique to a known device (method, or product) ready for improvement to yield predictable results; (e) "obvious to try" - choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success; (f) known work in one field of endeavor may prompt variations of it for use in either the same field or a different one based on design incentives or other market forces if the variations are predictable to one of ordinary skill in the art; and (g) some teaching, suggestion, or motivation in the prior art that would have led one of ordinary skill to modify the prior art reference or to combine prior art reference teachings to arrive at the claimed invention.

**Claims 1-7, 12-18, 21-23, 25-27, 29, 31, 37-38, and 43-44 over Ho**

The Examiner has rejected claims 1-7, 12-18, 21-23, 25-27, 29, 31, 37-38, and 43-44 over Ho. Specifically, the Examiner alleges that Ho teaches the present elements of independent claim 1. The Examiner then alleges that, even if each element is not present in Ho, Ho discloses the invention generally such that it would be obvious or the invention would be inherent from Ho's disclosure. The Applicant traverses the present rejection.

The Applicant renews the above arguments regarding Ho with respect to the present rejection. In short, the Applicant submits that Ho teaches a coordination complex between NTA-

modified PEO blocks (of Pluronic F108) with a metal and histidine-tagged proteins. To be clear, the coordination complex is shown in detail in Figure 1 of Ho and involves nitrilotriacetic acid groups, a metal ion, and two imidazole groups of the histidine tag on the protein. In other words, Ho does not teach a phenolic group or phenolic derivative of a first moiety that is cross-linked with a phenolic group or phenolic derivative of a second moiety. Rather, Ho teaches coordination between imidazole groups, a metal ion, and nitrilotriacetic acid groups. As such, the Applicant submits that Ho does not teach each and every element of the pending claims. Further, the Applicant submits that the present invention is not obvious over Ho as Ho uses an entirely different process which provides for a distinct and different resulting structure for its immobilization.

In light of the above, the Applicant submits that the Ho does not teach each and every element of claims 1-7, 12-18, 21-23, 25-27, 29, 31, 37-38, and 43-44. As such, the Applicant respectfully requests that the Examiner withdraw the present rejection.

Claim 1-24, 26-27, and 31-44 over Gill

The Examiner has rejected claim 1-24, 26-27, and 31-44 over Gill. Specifically, the Examiner alleges that Gill teaches the present elements of independent claim 1. The Applicant traverses the present rejection.

The Examiner alleges that Gill teaches phenolic metal ligands added to the first and second moieties and that such ligands are subsequently cross-linked. However, the Applicant respectfully disagrees. First, the Applicant notes that the present claims require 4 distinct steps: attaching a first metal ligand to a first moiety; attaching a second metal ligand to a second moiety, add a metal ion to form a coordinate complex between the first moiety and the second moiety, cross-linking the first and second moieties by exposing the coordination complex to an oxidizing agent to form a covalent crosslink between the phenolic groups or the phenolic derivatives. As such, the Applicant notes that the present method forms a coordination complex independently of the cross-linking of the phenolic or phenolic derivative groups. The Applicant submits that Gill does not teach each of the present steps.

Specifically, the Applicant submits that Gill does not teach attaching a first metal ligand to a first moiety or attaching a second metal ligand to a second moiety. Notably, Gill only discloses intermolecular coupling of RNases. In other words, Gill is taking existing compounds and crosslinking such compounds. Gill fails to disclose any step of adding first or second metal

ligand to its RNases.

The Applicant acknowledges that Gill discloses coupling of RNases using “accessible tyrosines on the surface of RNase.” Page 305, left column, bottom paragraph. However, the Applicant submits that such disclosure distinguishes the present method that specifically requires attachment of metal ligands before complexation and cross-linking.

Further, the Applicant notes that the mechanism provided in Gill is distinct from the present method. Specifically, Scheme 1 on page 307 shows a Ni ion coordinates the amide groups of consecutive amino acid groups within a single RNase compound allowing intramolecular electron transfer and subsequent intermolecular cross-linking. However, the Applicant notes that the present claims require “adding a metal ion to form a coordination complex between the first moiety and the second moiety.” The Applicant submits that the metal ion disclosed in Gill does not form a coordinate complex between a first and second moiety but forms a coordinate complex within a single moiety; i.e., the RNase as shown in Scheme 1.

In light of the above, the Applicant submits that Gill does not teach each and every element of claims 1-24, 26-27, and 31-44. As such, the Applicant respectfully requests that the Examiner withdraw the present rejection.

Claims 1-24, 26-29, and 31-44 over Stewart in view of Fancy

The Examiner has rejected claim 1-24, 26-29, and 31-44 over Stewart in view of Fancy. Specifically, the Examiner alleges that Stewart teaches the present elements of independent claim 1 but acknowledges that Stewart does not teach cross-linking phenolic or phenolic derivative groups. As such, the Examiner cites to Fancy as allegedly teaching cross-linking of HY-tags. The Applicant traverses the present rejection.

The Applicant notes that Stewart discloses similar subject matter as Ho (in fact each of the present inventors are listed on the Ho reference). For example, Figure 1 of Ho corresponds to Figure 1 of Stewart. As such, the Applicant submits that the comments with respect to Ho, as discussed above, are equally applicable in the present rejection. To be clear, the Applicant submits that Stewart teaches a coordination complex between NTA-modified PEO blocks (of Pluronic F108) with a metal and histidine-tagged proteins. FIG. 1; col. 3, lines 46-54; col. 7, lines 9-43. The coordination complex is shown in detail in Figure 1 of Stewart and involves nitrilotriacetic acid groups, a metal ion, and two imidazole groups of the histidine tag on the protein. In other words, Stewart does not teach a phenolic group or phenolic derivative of a first



moiety that is cross-linked with a phenolic group or phenolic derivative of a second moiety. Rather, Stewart teaches coordination between imidazole groups, a metal ion, and nitrilotriacetic acid groups.

The Examiner has acknowledged that Stewart does not teach cross-linking phenolic groups but cites to Fancy for such a teaching. However, Stewart specifically utilizes coordination rather than covalent cross-linking since one of Stewart's objectives is to have "reversible binding under non-denaturing conditions." Col. 2, lines 28-32. As such, the Applicant submits that utilizing cross-linking would destroy this explicit functionality as stated in Stewart. In other words, the Applicant submits that Stewart teaches away from the cross-linking presently claimed.

As the Applicant has raised the issue of teaching away, the Applicant would like to review the current case law regarding teaching away for the Examiner's convenience. The Court of Appeals for the Federal Circuit has clearly stated that "an applicant may rebut a prima facie case of obviousness by showing that the prior art teaches away from the claimed invention in any material respect." In re Petersen, 315 F.3d 1325, 1331 (Fed. Cir. 2003). The Court has also stated that "[w]e have noted elsewhere, as a 'useful general rule,' that references that teach away cannot serve to create a prima facie case of obviousness." (emphasis added) McGinley v. Franklin Sports, Inc., 262 F.3d 1339, 1354 (Fed. Cir. 2001). In identifying the appropriate standard for teaching away, the Court has further stated:

"A reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be **discouraged from following the path set out in the reference**, or would be led in a **direction divergent** from the path that was taken by the applicant. The degree of teaching away will of course depend on the particular facts; in general, **a reference will teach away if it suggests that the line of development** flowing from the reference's disclosure **is unlikely to be productive** of the result sought by the applicant." (emphasis added) In re Gurley, 27 F.3d 551, 553 (Fed. Cir. 1994).

Clearly in the present case, a person of ordinary skill in the art would be led in a path divergent from that taken by Applicant since Stewart specifically uses coordination, which is reversible, while the present invention provides for covalently bonding through cross-linking.

In light of the above, the Applicant submits that the combination of Stewart and Fancy is improper as Stewart teaches away from the present invention as well as Fancy. As such, the Applicant respectfully requests that the Examiner withdraw the present rejection.

**CONCLUSION**

In light of the above, Applicant respectfully submits that pending claims 1-44 are in condition for allowance. Therefore, Applicant requests that the rejections be withdrawn, and that the claims be allowed and passed to issue. If any impediment to the allowance of these claims remains after consideration of the above amendments and remarks, the Examiner is encouraged to call the undersigned at (801) 566-6633 so that such matters may be resolved as expeditiously as possible.

The Commissioner is hereby authorized to charge any additional fee or to credit any overpayment in connection with this Amendment to Deposit Account No. 20-0100.

DATED this 20<sup>th</sup> day of April, 2011.

Respectfully submitted,

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